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09/998,009	11/28/2001	Marina Konopleva	UTSC:652US	7245

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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/998,009	KONOPLEVA ET AL.	
	Examiner	Art Unit	
	James D. Anderson	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-33,36,37,40,41,44,45,48,49,52,53 and 56-66* is/are pending in the application.

4a) Of the above claim(s) *28-32* is/are withdrawn from consideration.

5)☒ Claim(s) *33,37,45,49,53 and 57-66* is/are allowed.

6)☒ Claim(s) *1,4,5,11-27,36,40,44,48,52 and 56* is/are rejected.

7)☒ Claim(s) *6-10* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10 sheets*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment filed 9/4/2007 and Information Disclosure Statement filed 8/14/2007 have been received and entered into the application.

Applicants' arguments, filed 9/4/2007, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Upon further consideration, the Examiner is applying new rejections to at least some of the pending claims. Accordingly, this Office Action is **Non-Final**.

Election/Restrictions

Claims 28-32 remain withdrawn from consideration as being drawn to non-elected subject matter.

Status of the Claims

Claims 1, 4-33, 36-37, 40-41, 44-45, 48-49, 52-53, and 56-66 are presented for examination. Claims 28-32 are withdrawn. Accordingly, claims 1, 4-27, 33, 36-37, 40-41, 44-45, 48-49, 52-53, and 56-66 are under examination and are the subject of this Office Action.

Information Disclosure Statement

Receipt is acknowledged of the information disclosure statement filed 8/14/2007. The Examiner has considered the reference cited therein to the extent that each is a proper citation. Please see the attached USPTO Form 1449.

Response to Arguments

Applicant's arguments filed 9/4/2007 have been fully considered and are persuasive in part. In the previous Office Action, claims 1, 4-27, 33, 36-37, 41, 44-45, 48-49, 52-53, and 56 were rejected under 35 U.S.C. § 112, 1st Paragraph (Scope of Enablement). The Examiner indicated that the claims were enabled for inducing cytotoxicity in leukemia cells but not for inducing cytotoxicity in solid tumor cells, killing tumor cells, inducing apoptosis in tumor cells, inducing differentiation in tumor cells, treating cancer (other than leukemia), potentiating the effect of a chemotherapeutic agent on a tumor cell or inhibiting the growth of a tumor cell by administering CDDO-Me in combination with any chemotherapeutic agent.

Firstly, Applicants argue that there is a significant body of literature on the use of CDDO and related compounds (*i.e.*, CDDO-Me) in the treatment of tumors other than leukemias, including breast, colon, pancreatic and ovarian cancers, thyroid carcinoma and metastatic melanoma. In support of this argument, Applicants cite ten non-patent literature articles. Two articles relating to CDDO-Me demonstrate that this compound is effective in inhibiting metastatic breast tumor growth (Ling et al., 2007) and treating thyroid carcinoma and metastatic melanoma (Dezube et al., 2007). Other cited articles demonstrate that the parent compound, CDDO, is effective against colon cancer, ovarian cancer, and pancreatic cancer, among others.

Accordingly, because CDDO-Me has been shown to be effective against leukemias, breast cancer, melanoma, and thyroid carcinomas, one skilled in the art would appreciate that CDDO-Me and a chemotherapeutic agent would likely be effective against other tumor cells (*e.g.*, solid tumors and leukemias). As such, the Examiner is persuaded that Applicants are enabled for the inducing cytotoxicity of cancer cells, but not for the broad scope of "inducing cytotoxicity in a cell" as recited in claims 1, 4-5, and 11-27.

Claim Rejections - 35 USC § 112 (2nd Paragraph)

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 23-24 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In the instant case, the Markush group recited in claim 23 indicates that a retinoid is selected from the group "comprising" all-*trans*-retinoic acid, 9-*cis*-retinoic acid, LG100268, LGD1069, fenretinide, and CD437, a RAR-specific retinoic acid and a RXR-specific retinoic acid. However, it is not clear what other retinoids may be a part of the recited group. The comprising language is open language indicating that there are other retinoids that may be part of the recited Markush group. Amending claim 23 to recite "....selected from the group *consisting of*..." would comply with proper Markush practice and overcome this rejection.

Claim Rejections - 35 USC § 112 (1st Paragraph)

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 22-23, 36, 40, 44, 48, 52, and 56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a Written Description rejection.

Regarding the requirement for adequate written description of chemical entities, Applicant's attention is directed to the MPEP §2163. In particular, *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089, 118 S. Ct. 1548 (1998), holds that an adequate written description requires a precise definition, such as by structure, formula, chemical name, or physical properties, "not a mere wish or plain for obtaining the claimed chemical invention." *Eli Lilly*, 119 F.3d at 1566. The Federal Circuit has adopted the standard set forth in the Patent and Trademark Office ("PTO") Guidelines for Examination of Patent Applications under the 35 U.S.C. 112.I "Written Description" Requirement ("Guidelines"), 66 Fed. Reg. 1099 (Jan. 5, 2001), which state that the written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics," including, *inter alia*, "functional characteristics when coupled with a known or disclosed correlation between function and structure..." *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 316, 1324-25 (Fed. Cir. 2002) (quoting *Guidelines*, 66 Fed. Reg. at 1106 (emphasis added)). Moreover, although *Eli Lilly* and *Enzo* were decided within the factual context of DNA sequences, this does not preclude

extending the reasoning of those cases to chemical structures in general. *Univ. of Rochester v. G.D. Searle & Co.*, 249 Supp. 2d 216, 225 (W.D.N.Y. 2003).

In the instant case, the claims recite the limitation "wherein said chemotherapeutic agent is a retinoid". As such, there are two criteria such compounds must fulfill: 1) the agent must treat cancer (*i.e.*, chemotherapeutic agent) and 2) the agent must be a retinoid (*i.e.*, chemically related to vitamin A). In claim 23, further limitations with respect to the claimed retinoids are recited. For example, the retinoid is a RAR-specific retinoic acid or RXR-specific retinoic acid. Aside from those retinoids recited in claim 23 (*i.e.*, all-*trans*-retinoic acid, 9-*cis*-retinoic acid, LG100268, LGD1069, fenretinide, and CD437), Applicants have failed to describe what retinoids possess the capability of being a chemotherapeutic agent and are RAR-specific or RXR-specific. Only one RXR-specific retinoic acid is described (*i.e.*, LG100268). Retinoids are broadly described in the art as being chemically related to vitamin A and are generally used to treat dermatological conditions such as acne and psoriasis. Whether or not any particular retinoid is chemotherapeutic cannot be predicted *a priori*. Accordingly, other than all-*trans*-retinoic acid, 9-*cis*-retinoic acid, LG100268, LGD1069, fenretinide, and CD437, Applicants have not adequately described the structural features of other retinoids that might be expected to have a chemotherapeutic effect. Similarly, the limitations RAR-specific retinoic acid and RXR-specific retinoic acid indicate that such retinoids specifically inhibit a particular receptor. However, other than LG100268, which is described as an RXR-specific retinoic acid, it is not apparent exactly what retinoids have activity that is specific for one receptor over another.

Claims 1, 4-5, and 11-27 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for inducing cytotoxicity tumor cells (e.g., solid tumors and leukemias), does not reasonably provide enablement for inducing cytotoxicity in "a cell" by administering CDDO-Me in combination with any chemotherapeutic agent. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This is a Scope of Enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fd. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

[1] As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence or absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art,

7) the predictability of the art, and

8) The breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

The nature of the invention: The invention relates to methods of inducing cytotoxicity in "a cell" comprising contacting said cell with CDDO-Me and a chemotherapeutic agent.

Relative skill in the art: The relative skill of those in the art is high, generally that of an M.D. or Ph.D.

State and predictability of the art: It is well established in the art that cells of different origin respond differently to different cytotoxic agents. An agent effective against a eukaryotic cell

may not be effective against a prokaryotic cell. CDDO-Me is a PPARγ ligand that inhibits the growth of tumor cells. However, it is not predictable that CDDO-Me would be effective in inducing cytotoxicity of any and all cells, regardless of their origin. The Examiner is unaware of any agent that induces cytotoxicity in cells of all types, including eukaryotic cells, prokaryotic cells, stem cells, mast cells, erythrocytes, fibroblasts, hepatocytes, neurons, oocytes, T-cells, myoblasts, etc. In fact, CDDO-Me was administered to human patients in a Phase I trial (Dezube et al., 2007) (cited by Applicants). If CDDO-Me were generally cytotoxic to all cells as in presently being claimed, it is highly unlikely that the patients in this trial would have survived the treatment.

The breadth of the claims: In the instant case, the claims are extremely broad insofar as they disclose the induction of cytotoxicity in any and all cell types, regardless of origin, via administration of the same compounds.

The amount of direction or guidance provided and the presence or absence of working examples: The specification provides no direction or guidance for determining the particular administration regimens (e.g., dosages, timing, administration routes, etc.) necessary to induce cytotoxicity in all cells, particularly in humans. Applicants have demonstrated that CDDO and CDDO-Me induce differentiation, inhibit cell growth and induce apoptosis in leukemia cell lines and in primary samples from AML patients (pages 83-92). Other literature references demonstrate that CDDO-Me induces cytotoxicity of solid tumors and leukemias. There is no evidence of record that CDDO-Me is cytotoxic to all cell types.

Sensitivity to CDDO-induced apoptosis correlated with levels of PPARγ. There is no evidence or reasonable expectation that the same effects observed in leukemia cells will also be observed in other cells, such as stem cells, mast cells, erythrocytes, fibroblasts, hepatocytes, neurons, oocytes, T-cells, myoblasts, etc.

Applicants have clearly demonstrated that PPARγ is expressed in myeloid cell lines and in primary AML, ALL and CLL samples. As such, one skilled in the art would reasonably expect the instantly claimed effects when CDDO-Me is administered to leukemia cell lines (and perhaps other cell lines that express PPARγ). However, given the mechanism of action and results demonstrated in the specification (and further in view of the prior and subsequent art), the skilled artisan would not reasonably expect that the instantly claimed combinations could be predicatively used to elicit the claimed responses in any cell line. Thus, the applicant at best has provided specific direction or guidance only for eliciting the claimed response in tumor cell lines. No reasonably specific guidance is provided concerning useful therapeutic protocols for any other cell lines.

The quantity of experimentation necessary: Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that the instantly claimed combinations (CDDO-Me + chemotherapeutic drug) could be predictably used to induce cytotoxicity in all cells as inferred in the claims and contemplated by the specification. Accordingly, the instant claims do not comply with the enablement requirement of 35 U.S.C. §

112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Allowable Subject Matter

Claims 33, 37, 41, 45, 49, 53, and 57-66 are allowed.

Claims are 6-10 objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would

like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

James D. Anderson
Patent Examiner
AU 1614

November 7, 2007

ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER